UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

MEMORANDUM

DATE: January 18, 2011

OFFICE OF CHEMICAL SAFETY
AND POLLUTION PREVENTION

SUBJECT: Science Review In Support of the Registration of Bug Oil Food Use containing Canola Oil, Tagetes Oil, Thyme Oil and Wintergreen Oil as its active ingredients.

Decision Number:	420839
DP Number:	396150
EPA File Symbol Number:	85937-E
Chemical Class:	Biochemical
PC Code:	011332, 176602, 597800, 176601, respectively
CAS Number:	120962-03-0, 8016-84-0, 8007-46-3, 68917-75-9, respectively
Tolerance Exemptions:	40 CFR 180.950 for all active ingredients
MRID Numbers:	48649801-48649813

FROM: Angela L. Gonzales, Biologist 1/18/12
Biochemical Pesticides Branch
Biopesticides & Pollution Prevention Division (7511P)

TO: Colin Walsh, Regulatory Action Leader
Biochemical Pesticides Branch
Biopesticides & Pollution Prevention Division (7511P)

ACTION REQUESTED

In response to the request for additional information discussed in the memorandum from A.L. Gonzales to C. Walsh dated 6/23/11 and relayed in a letter to the applicant dated 7/21/2011, the applicant has submitted a revised Confidential Statement of Formula (CSF) dated 11/3/2011, product chemistry information in MRIDs 48649801-48649813 and additional information in the cover letter and attachments dated 11/3/2011. An alternate formulation CSF dated 11/3/11 has also been submitted.

RECOMMENDATIONS AND CONCLUSIONS

1. The product chemistry submission is ACCEPTABLE, pending resolution of the deficiencies identified below.

MRID 48649801: ACCEPTABLE
MRID 48649802: ACCEPTABLE
MRID 48649803: ACCEPTABLE
MRID 48649804: ACCEPTABLE
MRID 48649805: ACCEPTABLE
MRID 48649806: ACCEPTABLE
MRID 48649807: ACCEPTABLE
MRID 48649808: ACCEPTABLE
MRID 48649809: ACCEPTABLE
MRID 48649810: ACCEPTABLE
MRID 48649811: ACCEPTABLE
MRID 48649812: ACCEPTABLE
MRID 48649813: ACCEPTABLE

Regarding Tagetes Oil:

a. All product chemistry data requirements for tagetes oil have been satisfied at this time.

Regarding Bug Oil Food Use:

a. Refer to the Confidential Appendix (CA) below.

b. Refer to the CA below.

c. All other product chemistry data requirements have been satisfied at this time.

2. The toxicology submission is ACCEPTABLE.

3. The nontarget organism toxicology submission is ACCEPTABLE.

STUDY SUMMARIES FOR BUG OIL FOOD USE

Product Chemistry (MRIDs 48649801, 48649803-48949805, 48649807-48649811, 48649813, cover letter attachments)

With the exception of the deficiencies discussed in the **Recommendations and Conclusions** section above, all product chemistry data requirements have been adequately satisfied. Refer to the Confidential Appendix (CA) below for additional information. Data Evaluation Records (DERs) were not created for the submitted MRIDs. The applicant confirmed that all ingredients in the formulation will be obtained only from the supplier(s) listed on the CSFs. Adequate data and information were submitted to satisfy the stability, UV/Visible light absorption, boiling point, vapor pressure and partition coefficient data requirements for thyme oil (MRIDs 48649803, 48649804, 48649807 and 48649813). Adequate data and information were submitted to satisfy the stability, UV/Visible light absorption and partition coefficient data requirements for canola oil (MRIDs 48649801, 48649805 and 48649811). The applicant submitted a response to the deficiencies identified in the storage stability study which is discussed in the CA below.

ADDITIONAL INFORMATION AND STUDY SUMMARIES FOR THE RISK ASSESSMENT FOR TAGETES OIL

I. Active Ingredient Characterization

A. Product Chemistry (MRIDs 48649802, 48649806, 48949812)

All product chemistry data requirements have been adequately satisfied for tagetes oil at this time. DERs were not created for the submitted MRIDs. The applicant confirmed that tagetes oil will be obtained only from the supplier listed on the CSFs. Adequate data were submitted to satisfy the stability, UV/Visible light absorption and partition coefficient data requirements. Although data were already submitted in MRID 47868202, additional boiling point data were submitted. The submitted physical and chemical data are summarized in Table 1 below.

TABLE 1. Physical and Chemical Properties of Tagetes Oil (40 CFR § 158.2030)

OPPTS Guideline No.	Property	Description of Result	MRID
830.6313	Stability to Normal and Elevated Temperatures, Metals and Metal Ions	Stable under normal and elevated temperatures for 14 days. No evidence of instability under contact with metals and metal ions for 14 days at ambient and elevated temperatures. Some color and physical state changes to the metal ions were observed during the study.	48649812
830.7050	UV/Visible light absorption	UV profiles are similar under all pH conditions. No significant molar absorbance (ε) at the wavelength range of 290-750 nm. Neutral pH: ε = 44.52, 45.98 at wavelength 237 nm Basic pH: ε = 40.13, 44.80 at wavelength 237 nm Acidic pH: ε = 45.38, 47.81 at wavelength 237 nm	48649806
830.7550 830.7560 830.7570	Partition Coefficient (n-Octanol/Water)	Values estimated using KOWWIN version 1.68 (US EPA) were submitted for the major components of tagetes oil, as the oil itself is not amenable to testing. Limonene: Log K_{ow} = 4.83 Ocimene: Log K_{ow} = 4.80 Dihydrotagetone Log K_{ow} = 2.92 Linalool Log K_{ow} = 3.38	48649802
830.7220	Boiling Point	170.5°C	48649806

II. Human Health Assessment

A. Toxicology (MRIDs 48329203, 48329205, 48339002)

Adequate mammalian toxicology data and information have been submitted to satisfy all of the Tier 1 toxicology data requirements at this time. The data and information presented in Table 2 below are a summary of the toxicity data and information submitted to support the new active ingredient, tagetes oil. DERs were not created for these MRIDs.

Table 2. Mammalian Toxicology Data Requirements for Tagetes Oil (40 CFR § 158.2050)			
Study/OPPTS Guideline No.	**Results**	**Toxicity Category/Description**	**MRID**
90-Day oral toxicity (870.3100)	Rationale was provided in lieu of a 90-day oral study. Tagetes oil is exempt from the requirement of a tolerance as a minimal risk active ingredient under 40 CFR 158.950(c). Significant exposure is not expected based on low application rates and rapid degradation in the environment. Tagetes oil is an edible oil and is already consumed in the human diet as it is used as a food additive in alcoholic beverages, baked goods, condiments, frozen dairy, gelatins, puddings, candy, and nonalcoholic beverages.		48339002
90-Day inhalation toxicity (870.3465)	Rationale was provided in lieu of a 90-day inhalation study. Significant repeat exposure to humans to tagetes oil as a gas, vapor or aerosol is not anticipated based in the use pattern. Additionally, significant exposure is not expected based on low application rates and rapid degradation in the environment.		48339002
Mutagenicity (Ames) (870.5100, 5300 and 5375)	Not mutagenic with or without metabolic activation in *Salmonella typhimurium* strains TA 98, TA 1537, TA 100, TA 1535 and *Escherichia coli* strain Wp2uvrA. Rationale was provided in lieu of an *in vitro* mammalian cell assay. Significant exposure to humans is not anticipated based on low application rates, appropriate PPE requirements on the label, and rapid degradation in the environment. Additionally, humans are already exposed to tagetes oil in the diet, as it is an edible oil and is used as a food additive in alcoholic beverages, baked goods, condiments, frozen dairy, gelatins, puddings, candy, and nonalcoholic beverages.		48329205
Developmental toxicity (870.3700)	Rationale was provided in lieu of a developmental study. Significant exposure to female humans is not anticipated based on low application rates, appropriate PPE requirements on the label, and rapid degradation in the environment. Humans are also already exposed to tagetes oil, as it is an edible oil and is used as a food additive in alcoholic beverages, baked goods, condiments, frozen dairy, gelatins, puddings, candy, and nonalcoholic beverages.		48339002

1. Acute Toxicity

All previously identified deficiencies have been adequately addressed. Please refer to the memoranda from A. L. Gonzales to C. Walsh dated 8/25/10 and 6/23/11 for additional information.

2. Subchronic Toxicity

90-Day Oral

Rationale was provided in lieu of a 90-day oral study. Tagetes oil is an edible oil and is exempt from the requirement of a tolerance as a minimal risk active ingredient under 40 CFR 158.950(c). Significant dietary exposure to humans is not anticipated based on low application rates and rapid biodegradation in the environment. Based on data provided in MRID 48329208, approximately 59% of tagetes oil volatilized (measured via weight loss) in 48 hours in a laboratory study. Additionally, tagetes is already consumed in the human diet, as it is used as a food additive. The Food and Drug Administration (FDA) has approved the use of the oil (in oil form only) with no limitations as a food additive under 21 CFR 172.510. Reported uses for tagetes oil are provided in Table 3 below.

Table 3. Reported Uses for Tagetes Oil as a Food Additive[1]

Food Category	Usual Amount (ppm)	Maximum Amount (ppm)
Alcoholic beverages	3.00	5.89
Baked goods	12.00	21.25
Chewing gum	4.42	4.42
Condiments, relishes	10.00	30.00
Frozen dairy	4.13	7.08
Gelatins, puddings	4.58	8.00
Hard candy	2.94	2.94
Nonalcoholic beverages	2.00	4.39
Soft candy	9.18	16.36

[1] Information from Fenaroli's Handbook of Flavor Ingredients (Burdock, 2005)

90-Day Inhalation

Rationale was provided in lieu of a 90-day inhalation study. Significant repeat exposure to humans to tagetes oil as a gas, vapor or aerosol is not anticipated based on the use pattern. Additionally, significant exposure is not expected based on low application rates and rapid degradation in the environment.

3. Developmental Toxicity and Mutagenicity

Rationale was provided in lieu of a developmental study. Significant exposure to female humans is not anticipated based on low application rates, appropriate PPE requirements on the label, and rapid degradation in the environment. Additionally, humans are already exposed to the oil in the diet, as the oil is edible and is used in a variety of foods as a food additive (refer to the discussion above). The Agency has also made the determination that because tagetes is an edible oil, residues of the oil are exempt from the requirement of a tolerance under 40 CFR 180.950(c).

In an Ames assay, concentrations of up to 5,000 µg/plate of tagetes oil were not mutagenic with or without metabolic activation (S9) in *Salmonella typhimurium* strains TA 98, TA 1537, TA 100, TA 1535 and *Escherichia coli* strain Wp2uvrA. Rationale was provided in lieu of an *in vitro* mammalian cell assay. Significant exposure to humans is not anticipated based on low application rates, appropriate PPE

requirements on the label, and rapid degradation in the environment. Additionally, humans are already exposed to the oil in the diet, as the oil is edible and is used in a variety of foods as a food additive (refer to the discussion above). The Agency has also made the determination that because tagetes is an edible oil, residues of the oil are exempt from the requirement of a tolerance under 40 CFR 180.950(c).

B. Dose Response Assessment

At this time, no endpoints have been identified; therefore, a dose response assessment is not required.

C. Food Quality Protection Act (FQPA) Considerations

1. Dietary Exposure and Risk Characterization

Significant dietary exposure to tagetes oil through use as a pesticide is not expected when label instructions are followed. The oil is used at low application rates and degrades rapidly in the environment. Humans are already exposed to the oil in the diet, as the oil is edible and is used in a variety of foods as a food additive (refer to Table 3 and the discussion above). The Agency has also made the determination that because tagetes is an edible oil, residues of the oil are exempt from the requirement of a tolerance under 40 CFR 180.950(c).

In the cover letter attachments, the applicant provided calculated estimates of potential residues using different scenarios based on label application rates, degradation of the active ingredient and time of harvest. While the information was informative, calculations were only provided for two crops, which is not realistically representative of the use pattern, as the product containing tagetes oil can be used on essentially any and all food crops.

2. Acute and Chronic Dietary Risks for Sensitive Subpopulations Particularly Infants and Children

Significant dietary exposure to tagetes oil through use as a pesticide is not expected when label instructions are followed. The oil is used at low application rates and degrades rapidly in the environment. Humans are already exposed to the oil in the diet, as the oil is edible and is used in a variety of foods as a food additive (refer to Table 3 and the discussion above). The Agency has also made the determination that because tagetes is an edible oil, residues of the oil are exempt from the requirement of a tolerance under 40 CFR 180.950(c).

D. Drinking Water Exposure and Risk Characterization

Residues of tagetes oil in drinking water are not expected when products are used according to label instructions. The active ingredient biodegrades rapidly in the environment (59% volatilization in 48 hours), is applied at low application rates and is not directly applied to water; therefore, residues of tagetes oil in drinking water are unlikely.

E. Occupational, Residential, School and Day Care Exposure and Risk Characterization

1. Occupational Exposure and Risk Characterization

An occupational exposure assessment was not conducted for tagetes oil, and is not required. Appropriate personal protective equipment (PPE) requirements on the label will mitigate any potential exposure to applicators and/or handlers. Additionally, no relevant toxicological endpoints have been identified. Based on the data and information available to the Agency, anticipated exposure is not likely to result in unreasonable risk to humans.

2. Residential, School and Day Care Exposure and Risk Characterization

Exposure to tagetes oil will be minimal in residential, school, and day care areas, as the product containing this active ingredient is intended for use on horticultural and agricultural crops.

F. Aggregate Exposure from Multiple Routes Including Dermal, Oral, and Inhalation

There is reasonable certainty that no harm to the US population will result from aggregate exposure to residues of tagetes oil. This includes all exposures for which there is reliable information. The Agency arrived at this conclusion based on the lack of toxicity of this active ingredient and the already widespread exposure without any reported adverse effects on human health. The risks from aggregate exposure via oral, dermal and inhalation exposure are a compilation of three low-risk exposure scenarios and are negligible.

G. Cumulative Effects

Pursuant to FFDCA section 408(b)(2)(D)(v), EPA has considered available information concerning the cumulative effects of tagetes oil residues and other substances that have a common mechanism of toxicity. No toxicological endpoints have been established for exposure to tagetes oil; therefore, cumulative effects with other substances that share a common mechanism of toxicity are not expected.

H. Risk Characterization

The Agency considered human exposure to tagetes oil in light of the relevant safety factors in FQPA and FIFRA. A determination has been made that no unreasonable adverse effects to the U.S. population in general, and to infants and children in particular, will result from the use of this active ingredient when label instructions are followed.

III. Environmental Assessment

A. Nontarget Organism Toxicology

All previously identified deficiencies have been adequately addressed. Please refer to the memoranda from A. L. Gonzales to C. Walsh dated 8/25/10 and 6/23/11 for additional information.

B. Environmental Fate and Groundwater Data

Environmental fate and groundwater data are not required at this time because the results of the nontarget organism toxicity assessment (Tier I data requirements) did not trigger these Tier II data requirements.

C. Ecological Exposure and Risk Characterization

Toxicity studies have not been submitted for tagetes oil. Rationale and data on the proposed EP have been submitted to fulfill these data requirements. According to the registrant, the active ingredients act synergistically; thus the combination of these chemicals is more potent as an insecticide than each ingredient alone. Therefore, the toxicological profile of the EP is germane to the risk assessment rather than the toxicological profile of tagetes oil alone. For registration of the proposed EP, the Agency has bridged the nontarget organism toxicology data from the EP to the TGAI, tagetes oil. The product is a contact insecticide that operates through a physical mode of action. The product is practically nontoxic to birds, fish and aquatic invertebrates and is not phytotoxic; toxic endpoints have not been identified for these species. The product is practically nontoxic via exposure through contact to nontarget insects. Based on the data submitted, the Agency has indicated in its review that the product may be moderately toxic via oral exposure to nontarget insects; however, no mortality was observed at the highest dose tested in the study. Additionally, significant oral exposure is not anticipated as the product is a contact insecticide and is expected to degrade rapidly in the environment. Toxic endpoints have not been identified for nontarget insects via the oral or contact route of exposure. The results of the submitted studies and screening-level risk assessment indicate that use of the product according to label instructions should not result in adverse effects to birds, fish, aquatic invertebrates, plants or nontarget insects.

REFERENCES

Burdock, GA. (2005). Fenaroli's handbook of flavor ingredients; adapted from the Italian language works of Giovanni Fenaroli, 5th edition. Boca Raton, Fl: CRC Press.

CONFIDENTIAL APPENDIX

RECOMMENDATIONS AND CONCLUSIONS

1. The product chemistry submission is ACCEPTABLE, pending resolution of the deficiencies identified below.

Regarding Bug Oil Food Use:

a. Regarding the changes in the container observed during the storage stability and corrosion characteristics study (MRID 48339001), the applicant proposed ways to remedy the container deformation such as adding label language regarding storage conditions, reducing the headspace in the container to ≤ 5% of volume, and/or adding small amounts antioxidants to the product formulation. The applicant must utilize the most effective remedy to prevent container deformation.

b. The applicant must provide the chemical name for the ingredient [redacted] in box 10 on the alternate formulation CSF. Additionally, the applicant must verify the composition of this ingredient (i.e.: inform the Agency if there are any other chemicals in the ingredient), as this information was not clear on the Material Safety Data Sheet (MSDS) provided.

STUDY SUMMARIES FOR BUG OIL FOOD USE

Product Chemistry (MRIDs 48649801, 48649803-48949805, 48649807-48649811, 48649813, cover letter attachments)

An acceptable storage stability study on the alternate formulation was submitted in MRID 48649808; the alternate formulation is stable for one year under ambient conditions. Physical and chemical properties on the formulation were also provided in this MRID and do not appear to vary significantly from the basic formulation. Effects to the product container (deformation of container) were observed in the corrosion characteristics study on the alternate formulation that were similar to the effects observed in the study conducted using the basic formulation. An explanation and potential remedies for this issue were provided in MRID 48649810. The applicant stated that the deformation was likely not due to degradation and/or chemical incompatibility of the packaging material with the formulation based on the lack of corrosion observed in the study and the lack of changes to the formulation itself. The applicant provided information that the likely cause of the deformation is the creation of a vacuum state in the container due to ester oxidation of the unsaturated fatty acids in canola oil, the primary component in the EP. An explanation was also provided indicating that although the container was altered due to the consumption of the oxygen in its headspace, the efficacy of the product is unlikely to change, as there were no changes (color, smell, viscosity, etc.) to the product itself during the study. The applicant proposed ways to remedy the container deformation such as adding label language regarding storage conditions, reducing the headspace in the container to ≤ 5% of volume, and/or adding small amounts

antioxidants to the product formulation. In the cover letter attachments the applicant submitted a response to the other deficiencies identified in the storage stability study provided in MRID 48339001. Regarding the 22.7% loss of wintergreen oil observed at one year, the applicant provided information and new data regarding the stability of the ingredient and variability in the studies, indicated that the loss is not expected to alter the efficacy of the product and proposed to expand the certified limits for the ingredient from ±10% to ±30%, which is acceptable (Refer to MRID 48649809). The applicant indicated that canola oil is not amenable to storage stability characterization because it is comprised of many components that can vary from sample to sample. Additionally, it was reported that when canola oil is rancid, there is a substantial odor and color change. Results of the new storage stability study on the alternate formulation (discussed below) indicate that there was no smell or color change after one year of storage.

cc: Angela L. Gonzales, Colin Walsh, BPPD Science Review File, IHAD/ARS
A. L. Gonzales, FT, PY-S: 1/18/12